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EXAMINER

LI, QIAN JANICE

ART UNIT	PAPER NUMBER
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1632

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/017,472

Applicant(s)

CHADA ET AL.

Examiner

Q. Janice Li

Art Unit

1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 2/2/04 & 3/18/04.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-25,32-43 and 68-77 is/are pending in the application.
- 4a) Of the above claim(s) 5,6 and 68-74 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4,7-25,32-43 and 75-77 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 07 December 2002 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4/5/04.
- 4) ☒ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

The amendment and response, Declaration of *Sunil Chada*, and supplemental amendment filed 2/2/04, 3/18/04, and 4/5/04 have been entered. It is noted that claims 44-67 had been canceled in the response submitted on March 17, 2003, but marked as "withdrawn" in the 3/18/04 submission. Appropriate correction is required.

In the 2/2/04 response, Applicants indicated that the withdrawal of claims 68-74 from consideration is inappropriate because they depend from the elected species in claim 32. In response, claims 68-74 are drawn to various fragments of SEQ ID No: 2 that differ from the elected species in length or sequence composition and thus are distinct from the elected species. Applicants are reminded that the elected species is directed to the amino acids 182-206 of SEQ ID No: 2 as indicated in the response submitted 7/7/03. Moreover, it is noteworthy that the dependencies of claims 68-74 are improper because the sequences of claims 68-74 encompass rather than further limit the sequence recited in claim 32. Accordingly, it is appropriate to withdraw these claims from consideration by the Examiner pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim.

Claims 1, 15-17, and 36 have been amended, and claims 75-77 are newly submitted. Claims 1-25, 32-43, and 68-77 are pending. Claims 1-4, 7-25, 32-43, and 75-77 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in 2/2/04 response would be addressed to the extent that they apply to current rejection.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 4/5/04 was filed after the mailing date of the first Office action on 9/30/03. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. However, the copending application 09/615,154 is not suitable to be listed in the face of a patent, thus, deleted from the PTO-1449.

Claim Objections

Claims 1, 13, 18-23, 36-38 stand objected to because they are drawn to an invention nonelected with traverse in the replies filed on 3/17/03 and 7/7/03. A complete reply to the final rejection must include cancelation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

In the 2/2/04 response, applicants traverse the objection citing the linking claim section in MPEP (809.03). This is not found persuasive for reasons below.

As an initial matter, it was indicated in the previous Office action mailed 9/30/03 and reiterated here, the restriction is not based on linking claim practice, the different groups of inventions are defined as independent and distinct inventions. Accordingly, the cited MPEP section does not apply to the instant restriction requirement.

Art Unit: 1632

Applicants are reminded of the rules in restriction practice, MPEP 802 states, "TWO OR MORE INDEPENDENT AND DISTINCT INVENTIONS MAY NOT BE CLAIMED IN ONE NATIONAL APPLICATION, EX-CEPT THAT MORE THAN ONE SPECIES OF AN INVENTION, NOT TO EXCEED A REASONABLE NUMBER, MAY BE SPECIFICALLY CLAIMED IN DIFFERENT CLAIMS IN ONE NATIONAL APPLICATION, PROVIDED THE APPLICATION ALSO INCLUDES AN ALLOWABLE CLAIM GEN-ERIC TO ALL THE CLAIMED SPECIES AND ALL THE CLAIMS TO SPECIES IN EXCESS OF ONE ARE WRITTEN IN DEPENDENT FORM (§ 1.75) OR OTHERWISE INCLUDE ALL THE LIMITATIONS OF THE GENERIC CLAIM". (37 CFR 1.141), and MPEP § 821.01 states "A COMPLETE REPLY TO THE FINAL REJECTION MUST INCLUDE CANCELATION OF NONELECTED CLAIMS OR OTHER APPROPRIATE ACTION (37 CFR 1.144)".

Claim 39 is objected to because it improperly depends from claim 36, and it appears claim 39 should depend from claims 37 and/or 38.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 7-25, 32-43 stand rejected and the rejection applies to new claims 75-77 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for intratumoral injection of a nucleic acid expressing full length MDA-7 polypeptide or secreted form of MDA-7 (lacking a secretion signal) for treating angiogenesis-dependent cancer, does not reasonably provide enablement for distal or systemic administration of an adenoviral vector expressing *fragments* of MDA-7

polypeptide for treating angiogenesis-dependent tumor, for reasons of record and following. Applicants' arguments would be addressed below in the order they were presented.

1. MDA-7 fragments:

Applicants assert that the cited references do not support the conclusion of the Office action. Applicants argue that the Rudinger reference is almost 25 years old, does not reflect the state of the art at the time the application was filed. Applicants also argue that the entire Skolnick paper is focused on the issue of predicting a protein's function when only sequence information is available, whereas in the instant case, a function for MDA-7 is already provided, and a skilled artisan could readily prepare fragments covered by the claims.

The arguments have been fully considered but found not persuasive. This is because the specification and the prior art of record only disclose the function of a full length MDA-7 protein with or without a secretory signal, yet the claims encompass any truncated MDA-7, such as fragment 182-206 of SEQ ID No: 2, and any fragment ranging from 10 to 206 contiguous amino acids of SEQ ID No: 2 (Specification, page 13, lines 16-20, for example). Neither the specification nor art of record, teaches a consensus region that is critical for the function of MDA-7 fragments or teaches the structural correlation of the MDA-7 fragments with its function for inhibiting growth of tumor cells or for inhibiting angiogenesis. Apparently, the specification relies on the state of the art for support of enablement. This is why the Office cited three general art of record (Bowie et al, Skolnick et al and Rudinger) to illustrate the state of the art with

Art Unit: 1632

respect to the sequence structure and protein function. The references are relevant because the claimed subject matter is directed to using a modified protein (truncated MDA-7) and its presumed function as equivalent to the function of the unmodified protein (full length MDA-7 with or without a secretory signal), however, not a single fragment beyond the secreted form of MDA-7 is disclosed as functional equivalent to the full length MDA-7, and the art of record teach that the function of a modified protein is often unpredictable. Hence even though one can prepare these fragments, it requires undue experimentation for determining the function of the fragments encompassed by the claims. The Federal Circuit has stated that:

a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, **when there is no disclosure of any specific starting material** or of any of the conditions under which a process can be carried out, **undue experimentation is required**; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1005 (CAFC 1997) (emphasis added).

Thus, it is applicants' duty to provide an enabling teaching for the claimed invention commensurate in scope with the claims.

In response to applicant's argument based upon the age of the references, contentions that the references are old are not impressive absent a showing that the art tried and failed to solve the same problem notwithstanding its presumed knowledge of

Art Unit: 1632

the references. See *In re Wright*, 569 F.2d 1124, 193 USPQ 332 (CCPA 1977). In the instant case, the cited references published in a period ranging from 1976 to 2000, which indicate even with the advance of biotechnology, the basic principle taught by *Rudinger* 25 years ago is still applicable to the state of the art as of year 2000. Thus, specific guidance is required with respect to using fragments of MDA-7 for achieving a cancer-killing effect. It is noted aside from a secreted form of MDA-7 (lacking a secretion signal), not a single truncated form of MDA-7 is disclosed in the specification and it is also noted that in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 38 USPQ 189 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Goodman*, 29 USPQ2d 2010 (CA FC 1993); *In re Fisher*, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. *In re Dreshfield*, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "IT IS WELL SETTLED THAT IN CASES INVOLVING CHEMICALS AND CHEMICAL COMPOUNDS, WHICH DIFFER RADICALLY IN THEIR PROPERTIES IT MUST APPEAR IN AN APPLICANT'S SPECIFICATION EITHER BY THE ENUMERATION OF A SUFFICIENT NUMBER OF THE MEMBERS OF A GROUP OR BY OTHER APPROPRIATE LANGUAGE, THAT THE CHEMICALS OR CHEMICAL COMBINATIONS INCLUDED IN THE CLAIMS ARE CAPABLE OF ACCOMPLISHING THE DESIRED RESULT."

Applicants go on to cite Marzocchi to argue that the PTO has not provided acceptable evidence or reasoning to suggest the specification as a whole is not enabling. In response, it is noted that *Marzocchi* also states "IN THE FIELD OF CHEMISTRY GENERALLY, THERE MAY BE TIMES **WHEN WELL-KNOWN UNPREDICTABILITY OF CHEMICAL REACTIONS WILL ALONE BE ENOUGH TO CREATE REASONABLE DOUBT** AS TO ACCURACY TO **BROAD STATEMENT** PUT FORWARD AS ENABLING SUPPORT FOR CLAIM; THIS WILL ESPECIALLY BE THE CASE WHERE STATEMENT IS, ON ITS FACE, CONTRARY TO GENERALLY ACCEPTED SCIENTIFIC PRINCIPLES, ETC" (*In re Marzocchi and Horton*, 169 USPQ 367 CCPA1971, emphasis added). The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). When instant claims read on a method for the treatment of any angiogenesis-associated disease, which encompasses a broad array of diseases such as recited in claims 3 and 77 using a polypeptide whose sequence differs markedly from the known polypeptide (e.g. a ten-mer truncation vs. >200 mer full length), a doubt is reasonable. Furthermore, the Office has provided numerous teachings such as *Bowie et al*, *Skolnick et al* and *Rudinger* to illustrate the state of the art and the levels of those skilled artisans to indicate the doubt is reasonable.

Applicants then argue that they have provided additional evidence regarding a MDA-7 polypeptide lacking the first 48 amino acids in the declaration of Sunil Chada. In response, it is noted that said polypeptide is the full length MDA-7 lacking a secretion signal (the secreted form of MDA-7), and the Declaration shows that two of the four polypeptides do not have cancer-killing effects, the other two that function in killing cancer cells are full length MDA-7 or MDA-7 lacking a secretion signal and targeted to ER. All MDA-7 polypeptides tested in the specification or the Declaration contain the full

Art Unit: 1632

length or full length lesser a secretion signal, which is not a representative species of the truncated fragments ranging from 10-206 contiguous amino acids of SEQ ID No: 2 as instant claims encompass. Accordingly, the specification fails to provide adequate support for the full scope of the claims.

2. Secretory signal with MDA-7:

In view of the Declaration and example 3 of the specification, this portion of the rejection is withdrawn because the disclosure has shown the MDA-7 lacking a secretion signal has cancer-killing effect.

3. The routes of administration:

Applicants content that the cited references do not support the conclusion of the Office action, the arguments are addressed below.

i) Gene therapy: Applicants argue that the citation to Miller and Boucher is irrelevant because they both involve statement to the treatment of cystic fibrosis, while the present invention is related to inhibiting angiogenesis. Applicants further indicate that they are not clear why the statement of Makrides would indicate that undue experimentation would be required to practice the instant invention.

The arguments have been fully considered but found not persuasive for reasons of record and following. Claims broadly encompass administering a (*any*) nucleic acid, naked or in any type of vector, particularly adenoviral vector encoding mda-7 through regional and systemic delivery from a site *distal* from the site of the disease. However,

Art Unit: 1632

the specification fails to teach how the nucleic acid could reach the target site in a sufficient amount so that a therapeutic effect of tumor killing or inhibiting angiogenesis could be achieved. Regardless the type of diseases being treated, gene therapy first requires delivering a therapeutic gene to the site of target. Although the specification provided intratumoral route of delivery, and contemplated other routes of delivery, a review of the art of record indicated that gene targeting to desired cells and tissue has yet to become routine in the art. *Deonarain* was cited to illustrate this fact. *Miller* reference was cited to illustrate that while there are many vectors known in the art that can be used for gene delivery, no single vector is considered to be universally appropriate, thus, when claiming a method of treating angiogenesis anywhere in the body, for any type of angiogenesis or tumor, specific but not general guidance is necessary. Moreover, the very citation of *Miller* compared the delivery of vectors for treating cancer and cystic fibrosis, indicating the teaching is completely relevant to the instant claims. In the same citation, *Miller* also teaches that because of the under-developed state of the vector targeting, gene therapy as represented by cystic fibrosis has largely relied on the localized delivery. The applicability of the teaching has been seen in the instant disclosure where the anti-tumor effect of Adv-MDA-7 was achieved by localized (intratumoral) delivery in the working examples of the specification and in the subsequently submitted declaration. The *Makrides et al* reference was cited to provide further reasoning as to the association between the choice of vector system and production of a therapeutic protein, subsequently the efficacy of the treatment. *Boucher et al* reference was cited to evidence that in addition to the choice of the vectors,

another critical element to the success of gene delivery is the host resistance to foreign gene transfer. Although the focus of the publication is gene therapy for CF, the fact that host cells have innate ability to defend themselves against the penetration of gene therapy vectors is generally applicable to vector delivery, thus, relevant to the enablement of the instant claims.

Applicants then argue that examples 1, 4, 6, 9-11 and the newly submitted declaration support the contention that the claims are enabled. In response, all of the examples in the specification and the declaration are either *in vitro* experimentation or uses a localized *in vivo* delivery approach, and the specification fails to teach how the vectors could reach the site of target from distance in a sufficient amount so that a therapeutic effect could be achieved when claims encompassing using any type of nucleic acid expressing human MDA-7 for treating any angiogenesis and cancer.

Thus, it is evident that at the time of the invention, the gene therapy practitioner, while acknowledging the significant potential of gene therapy for angiogenesis and cancer, still recognized that such therapy was neither routine nor accepted, and awaited significant development and guidance for its practice. Therefore, it is incumbent upon applicants to provide sufficient and enabling teachings within the specification for such therapeutic regimen. Although the instant specification provides a brief review of a potential therapeutic use of the claimed method and data from *ex vivo* and animal studies, it is not enabled for its full scope because the specification does not disclose the structure-functional relationship of MDA-7 fragments, and fails to teach whether the

nucleic acids encompassed by the claims would function properly *in vivo* by any means of delivery, particularly delivered from a distal site.

ii). Nonviral-vector: Applicants assert that Deonarain reference does not support the broad conclusion that gene therapy with non-vial vector nucleic acids is unpredictable and inefficient because the citation has been taken out of context and because Deonarain acknowledges the viral methods of gene delivery in the next sentence and discussing the need for alternative methods relating to mutagenesis side effects and toxicity, not targeting and expression levels.

The arguments have been fully considered but found not persuasive. As an initial matter, Deonarain reference was cited to evidence the importance of gene targeting, not to make the conclusion as applicant asserted. To this end, it is undeniable that the *Deonarain* publication is devoted to targeted gene delivery with ligands. As the subtitle (given by the applicants) indicated, the strategy is particularly useful for non-viral vector delivery, thus, even though *Deonarain* acknowledges the efficiency of viral vectors in gene delivery, they clearly pointed out the need for alternative methods, i.e. non-viral vector delivery because of the mutagenesis side effects and toxicity of the viral vectors. They clearly pointed out the need for including targeting mechanism for non-viral vector delivery. Throughout the publication, the author repeatedly teaches the state of the art in general transgene delivery. For example, in addition to the previous citation, "GENE DELIVERY REMAINS THE MAJOR TECHNOLOGICAL STUMBLING BLOCK IN GENE THERAPY STRATEGIES" (2nd paragraph, page 54), and "IN ORDER TO ACHIEVE THE LEVELS OF GENE TRANSFECTION AND EXPRESSION SEEN WITH RETROVIRAL VECTORS, FURTHER ADVANCES NEED TO BE MADE IN FIELDS

SUCH AS MAMMALIAN ARTIFICIAL CHROMOSOMES" (paragraph bridging pages 65-66). It is noted that the teaching cited by applicants in the conclusion of the *Deonarain* ("under optimal conditions...") spoke an ideal condition not yet realized, and was preceded with the teaching, "PRESENTLY, THIS APPROACH TO GENE DELIVERY IS MUCH LESS EFFICIENT THAN VIRAL GENE DELIVERY".

Applicants go on to argue that the reference concerns specifically one type of nonviral vector, i.e. ligand-targeted receptor mediated vectors as recited in the title of the reference. In response, the title states the general strategy for any non-viral vector gene delivery, is not limited to a particular type of non-viral vector. Again, the reference was cited to evidence the necessity for gene targeting. Applicants also content that even if a particular type of gene therapy is still undergoing experimentation and improvement that does not mean that instant claims are not enabled. In response, the rejection is a scope one, the nucleic acids are enabled for intratumoral delivery but not systemic or distal delivery as discussed on record.

Moreover, applicants content that the concern of vector targeting may be less significant for a gene such as mda-7 because it selectively induces apoptosis in cancer cells as opposed to normal cells. While this is known, it remains critical to have sufficient amount of transgene reach the site of the target in order to achieve a therapeutic effect as claimed.

iii). Viral vectors: Applicants contend that the office does not cite a reference or provide declaration to support the contention that the tissue tropism of adenovirus is respiratory epithelial cells. Applicants also argue that literature replete with example of

Art Unit: 1632

adenovirus infecting a variety of cell types. In response, the challenged fact is well known in the art, and can be easily found in the cited references of record. For example, *Miller et al* teach that adenoviral diseases are usually associated with respiratory epithelium, although their receptor could be found in other cells and tissue, the degree of such tropism is limited (paragraph bridging pages 192-3). In figure 1 of *Boucher* reference, the adenoviral receptor CAR was illustrated in the surface of airway epithelia. Applicants are reminded that the reason of tissue tropism of adenovirus has been brought to attention is because if the viral vectors are administered systemically from a site distal from tumor, it may require a targeting mechanism so that sufficient amount of transgene could reach the site of targeted tumor. Applicants are also reminded that they use adenoviral vectors transfected breast cancer cells (example 4) because they use a localized delivery method or *in vitro* experimentation where targeting is not an issue, applicants have not disclose a single case that the angiogenesis was inhibited by a distal delivery. Thus, in view of the levels of the skilled in the art, the claimed invention does not appear to be enabled commensurate in scope with the claims.

Accordingly, in view of the quantity of experimentation necessary to determine the parameters for achieving *in vivo* gene expression in selected cells at therapeutic levels, in particular with any fragment of MDA-7, any type of nucleic acids, via any routes of administration, the lack of direction or guidance provided by the specification as well as the absence of working examples with regard to targeted *in vivo* gene therapy with fragments of MDA-7 delivered by regional and systemic routes, and the breadth of the claims directed to the use of numerous fragments, it would have required

undue experimentation for one skilled in the art to make and/or use the claimed invention.

Accordingly, the rejection stands.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 9 stand rejected, and claims 1-4, 7-25, 32-42, 75-77 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Concerning claim 9, Applicants argue that “pfu” is used in the literature, and submitted two references to support the argument. In response, the issue here is not about whether or not “pfu” is used in the literature but clarity of the claims. In the submitted references, the phrases concerning pfu are “following intraperitoneal challenge with 5000 PFU of virulent JEV” (Klein et al) and “inoculated with doses of Seoul virus ranging from 10^{-4} to 10^6 PFU” (Chang et al). Thus, it is clear that it refers to the total does administered in a subject, whereas claim 9 as written, the recited “pfu” could be the concentration of the viral stock solution, i.e. “pfu per mL”, or the viral concentration in the infected cell, i.e. “pfu per cell”, or the total does for each individual. It is unclear which meaning the applicants intend to claim, and thus the metes and bounds of the claim are uncertain.

Art Unit: 1632

Claim 1 is vague and indefinite because it is incomplete. The amended claim 1 replaces the "whereby" phrase with the phrase of "to inhibit angiogenesis", which only states the goal of the method that has been stated in the preamble. This amendment renders the claim indefinite because it is unclear whether the goal of the method stated in the preamble has been resolved.

Claims 15-17 recite the limitation, "the injection". There is insufficient antecedent basis for this limitation in the claims.

Claims 75 and 76 recite the limitation "viral particles". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 7, 8, 10-15, 24, 25, 35, 36, 42, 43 stand rejected and the rejection applies to new claim 77 under 35 U.S.C. 102(e) as being anticipated by *Fisher* (US 6,355,622).

Claim 77 further defines the type of angiogenesis-dependent cancer, which has been taught by *Fisher et al* (e.g. column 5, lines 20-25).

Applicants argue that *Fisher et al* does not even mention angiogenesis or inhibition of angiogenesis, accordingly, it does not anticipate the claimed invention.

The argument has been fully considered but found not persuasive. As an initial matter, Applicants are reminded that the *elected species* for a disease is drawn to angiogenesis-dependent cancer. This is reflected in the claims, which recite a method of inhibiting angiogenesis in a human subject in need of such treatment (claim 1), wherein said patient exhibits an angiogenesis-related disease (claim 2), wherein said disease is further defined as angiogenesis-dependent cancer (claim 3), which encompasses any solid tumor, leukemia, or any tumor metastasis (claim 4). Clearly, *Fisher et al* teach inhibiting angiogenesis dependent cancer (e.g. column 5, lines 32-43) even though they do not choose using the term “angiogenesis”, which is a well-known condition associated with cancer. For example, the specification (page 110) cites *Folkman et al* (1990), who teaches the evidence that tumors are angiogenesis dependent. Accordingly, *Fisher* anticipates the instant claims.

Claims 1-4, 7-25, 35-43 stand provisionally rejected and the rejection applies to new claims 75-77 under 35 U.S.C. 102(e) as being anticipated by copending Application No. 09/615,154 which has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the copending application, it would constitute prior art under 35 U.S.C. 102(e), if published under 35 U.S.C. 122(b) or patented. This provisional rejection under 35 U.S.C. 102(e) is based upon a presumption of future publication or patenting of the copending application.

Applicants indicate that they will address this rejection once one of the applications becomes otherwise allowable. Until then, the rejection stands.

Claims 1-4, 7-25, 35-43 stand rejected and the rejection applies to new claims 75-77 under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. U.S. patent application 09/615,154 has a different inventive entity, yet the disclosure anticipates the instantly claimed invention.

Applicants fail to address this rejection, thus, for reasons of record, the rejection stands.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 7-9, 20-23, 36-41 stand rejected and the rejection applies to new claims 75 and 76 under 35 U.S.C. 103(a) as being unpatentable over *Roth et al* (US 6,069,134), in view of *Fisher* (US 6,355,622), for reasons of record and following.

Claims 75 and 76 are drawn to the total dose of viral vectors applied to the individual ranging from 10^{10} to 10^{13} . *Roth et al* teach administering adenoviral particle at an m.o.i. of 10^8 pfu/ml, did not mention the total viral particles, and *Fisher et al* teach the end m.o.i. should be 10^2 pfu/cell, did not mention the total viral particles. Although *Roth*

Art Unit: 1632

or *Fisher* uses different criteria for calculating the amount of viral vector administration, it would have been obvious to one of ordinary skill to figure out a proper amount of viral vectors needed for achieving therapeutic effects. Accordingly, these limitations fall within the bound of optimization.

In the 2/2/04 Remarks, Applicants first argue that claim limitations are not taught by the combination of references because neither Roth nor Fisher mentions angiogenesis.

In response, as discussed above, claims are clearly drawn to a method of inhibiting angiogenesis in a human subject in need of such treatment, wherein said patient exhibits an angiogenesis-related disease (claim 2), wherein said disease is further defined as angiogenesis-dependent cancer (claim 3), which encompasses any solid tumor, leukemia, or any tumor metastasis (claim 4). Clearly, inhibiting angiogenesis encompassing inhibiting tumor, which has been clearly taught by *Fisher et al* (e.g. column 5, lines 32-43) or *Roth et al* (e.g. abstract, column 3, lines 20-48). even though they do not choose to use the term "angiogenesis".

Applicants then argue that there is no reasonable expectation of success as neither reference discusses angiogenesis, the skilled artisan would not have any reason to believe that combining the teachings of the references would provide a way to inhibit angiogenesis in a patient.

In response, the instant claims clearly indicated that the recited angiogenesis encompasses cancer angiogenesis, which is the elected species for the type of diseases, and it is well known in the art that tumors are angiogenesis dependent.

Art Unit: 1632

Accordingly, since *Fisher et al* taught the success of inhibiting tumor with a nucleic acid expressing MDA-7, a reasonable success is expected in inhibiting the angiogenesis by suppressing the tumor growth. Accordingly, the rejection stands.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 7-25, 32, and 35-43 stand provisionally rejected and the rejection applies to new claim 77 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 91-116, 125-154, 159-174 of copending U.S. Patent Application No. 09/615,154.

Applicants indicate that they will address this rejection once one of the applications becomes otherwise allowable. Until then, the rejection stands.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

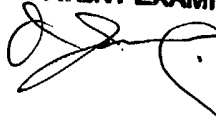
Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Art Unit: 1632

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist **Rena Jones** whose telephone number is **571-272-0571**.

Q. Janice Li
Patent Examiner
Art Unit 1632

JANICE LI
PATENT EXAMINER



QJL

June 14, 2004